GENERIC PHARMACEUTICAL INDUSTRY ASSOCIATION

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Alice E. Till, Ph.D.
President

April 27, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5600 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Draft Guidance for Industry on ANDAs: Impurities in Drug Products [Docket No. 98D-1168]

Dear Sir/Madam:

On behalf of the Science Committee of the Generic Pharmaceutical Industry Association (GPIA), I would like to submit comments to you on "Draft Guidance for Industry on ANDAs: Impurities in Drug Products", 64 FR 516, January 5, 1999.

GPIA is comprised of the manufacturers and distributors of generic medicines (as well as the providers of technical services and goods to these firms). Many of our members will be directly impacted by implementation of the final guidance on impurities in drug products for ANDAs.

The attached comments represent two primary concerns with the requirements embodied in the draft guidance: Identifying and reporting degradation products (line 76); and, qualification procedures, comparative chromatographic studies (line 215).

We would appreciate your consideration of these concerns as the draft guidance is finalized.

Sincerely,

Alice E. Till, Ph.D.
President

CC S. Hyden, Chair GPIA Science Committee
M. Hsiao, Chair GPIA Taskforce on Impurities

Line 76:

Degradation products observed in stability studies conducted at recommended storage conditions should be identified when the thresholds proposed in Attachment A, Table 1, are equaled or exceeded.

Comments:

Accelerated stability studies are conducted at 40 ° C / 75% RH for 3 months. If significant change occurs, testing is conducted at 30 ° C / 60% RH for 12 months. Accelerated stability data is used to establish a tentative two year expiration date which must be confirmed by studies at 25° C / 60% RH for 2 years. The labeling for products intended to be stored at room temperature is Store at 25° C (77° F) excursions permited to 15 - 30° C (59-86° F).

The Guidance makes no mention of a case where a degradation product is observed at 40° C, but is not observed at lower temperature studies. If a degradation product is formed at 40° C, but does not form during stability studies when the drug product is stored at conditions that will be required by the product labeling, there should not be a requirement to identify the degradation product.

Line 215:

To obtain meaningful comparison of degradation profiles, it is important that any comparative stability studies be conducted on fresh batches of each product or, if possible, the dates of manufacture of the generic drug product should precede those of the corresponding RLD batches.

Comments:

While this appreoach may yield a comparison of the relative rates of degradation, it does not provide meaninful data as to the level of the degradation product that has been qualified in the RLD, or what an appropriate specification should be. A comparative profile tells one is that at any given time after manufacture, what the relative amounds of the degradation product are likely to be. In addition, "fresh batches" are hard to define, or obtain with assurance, when RLC may have shelf lives as long as five years.

Many degradation mechanisms are not linear. For example, they may be self catalyzing. Thus, the amound of degradation product that the patient population has been exposed to, qualifying that level, may not be accurately estimated from relatively shor term comparative accelerated stability studies.

From a patient safety point of view, it does not matter at what rate the degradation product formed, only the amound of degradation product present in the product when it is used. By definition, the amount of degradation product formed in the RLD, at the end of shelf life (expiration), has been qualified. This level should be used to construct both a meaningful and equitable specification that benefits all: the patient, the reference listed product producer, and the genric product producer.

Therefore, we recommend that this section be rewritten to specify that three lots of the RLD at or near the expiration date be tested for the levels of degradation product present. And that a specification for that degradation product be based on not more than two times that qualified level.